

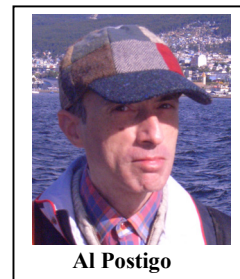
## REVIEW ARTICLE

## Transition Metal-free Photoorganocatalytic Fluoroalkylation Reactions of Organic Compounds

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**Abstract:** The generation of perfluoroalkyl radicals ( $R_F^\bullet$ ) by means of photocatalysis is a more suitable route than the established methods employing chemical initiators, like azo or peroxide compounds or the use of transition metals. Conditions governed by photocatalysis can allow for a wide range of functional groups and, therefore, can be applied to the late-stage transformation of bioactive molecules. Organic photocatalysts (POC), in the absence of transition metals, can suffer electron-exchange reactions, yielding  $R_F$  radicals.  $R_F$  radical production without the assistance of transition metals through the employment of POC will be described, applying this methodology to studying classical examples.



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## ARTICLE HISTORY

Received: April 28, 2016

Revised: May 20, 2016

Accepted: June 12, 2016

DOI:  
10.2174/1385272820666160614080  
432**Keywords:** Photo-organocatalysis, fluoroalkyl radicals, organic dyes.

## 1. INTRODUCTION

Photoorganocatalysts can harbour enough energy in their excited states to allow the build-up of reactive intermediates through atom transfer or redox processes [1]. Thermal barriers, which are ordinarily surmounted through the use of harsh reagents or extreme reaction conditions, can be replaced by the very excited state potential energy surfaces that excited POCs can reach. Catalysts such as those from the ruthenium and iridium salts have innate toxicity, and their availability and costs are disadvantages of the metal-based methods. By using green light, red to orange dyes could be employed to perform photoredox catalysis successfully. Enzymatic processes as well as organocatalysis can both achieve asymmetric catalysis, for which the latter should be considered a valid recourse when designing stereocontrolled syntheses [1b,c]. Photoorganocatalysis has recently been reviewed [1d]. However, perfluoroalkylation reactions by photoorganocatalysis are scarce in the literature. In

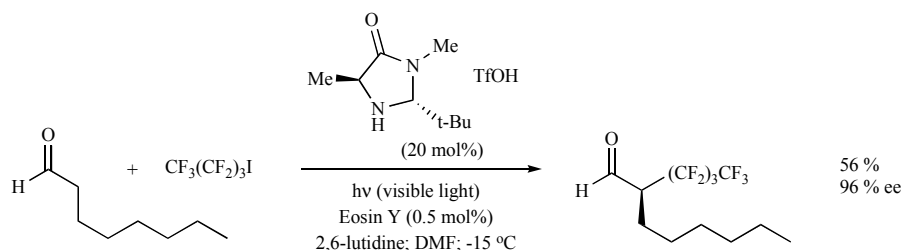
ety in the structural organic backbone will be studied. POCs employed as organic dyes can have structural motifs derived from aromatic ketones, quinones, heterocycles [1a]; the commonly encountered intermediates are radicals, and radical ions; the substrates are alkanes, alkenes, amines, ethers, etc. The salient feature of the method is the soft formation of reactive intermediates under benign conditions.

## 2. PHOTOORGANOCATALYSIS (POC)

## 2.1. Fluoroalkylation of Aliphatic Systems by Photoorganocatalysis

2.1.1. Fluoroalkylation of  $sp^3$  Carbon Atoms by Photoorganocatalysis

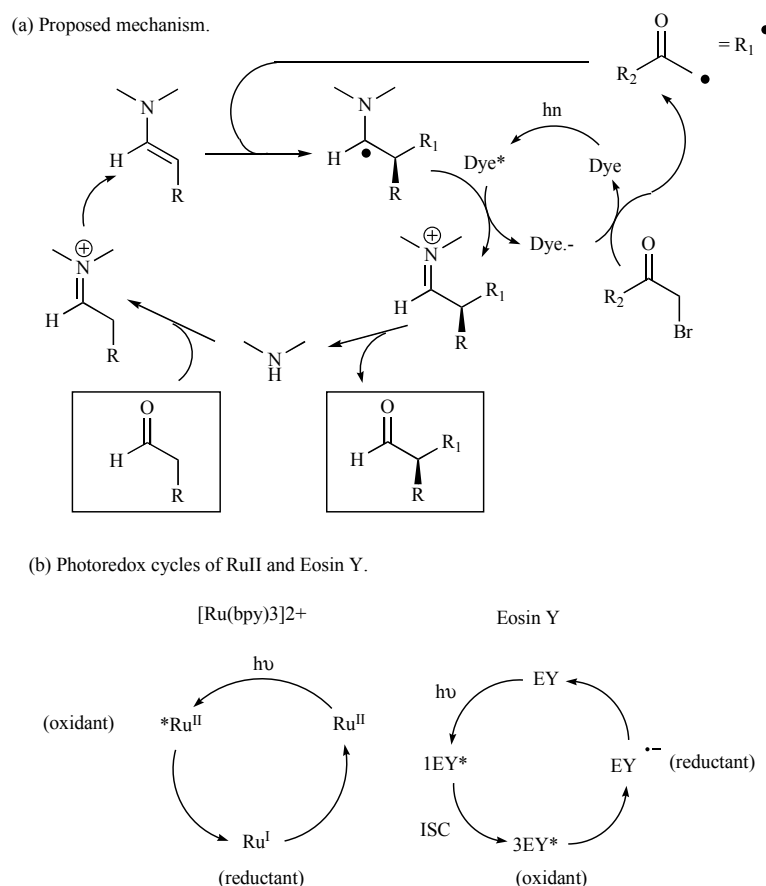
The stereospecific attachment of perfluoroalkyl substituents on aliphatic aldehydes has been introduced by Zeitler and collaborators [2a] (Scheme 1).

**Scheme 1.** Stereocontrolled  $\alpha$ -polyfluorination of aliphatic aldehydes.

these review, reactions where through irradiation a substrate catalyzes a process and provokes the introduction of a fluoroalkyl moi-

The mechanism of this reaction has not been clarified yet [2]. The suspected mechanism consists of visible light excitation of POC eosin Y (photoredox catalyst), which after fast intersystem crossing to its more stable triplet state, enables electron transfer (ET; Scheme 2) [2a]. Analogously to the chemistry of  $Ru^{2+*}$ , excited eosin Y ( $^3EY^*$ ) can undergo reductive and oxidative processes

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**Scheme 2.** Excited eosin Y involved in reductive and oxidative quenching cycles.

[3, 4]. These results resemble those from MacMillan and coworkers; it is observed that eosin Y can act as a reductant—with the aid of the sacrificial donor (*i.e.*: enamine) [5]—to afford the electron-deficient alkyl radical by means of ET with an alkyl halide. Addition of this radical to the electron-rich enamine (formed in the catalytic cycle) merge the activation pathways. The electron for the reductive quenching of the excited state of the dye  $^3\text{EY}^*$  is provided by the oxidation of the amino radical to the iminium species in the catalytic cycle [6, 2]. Next, the authors paid attention to the determination of the quantum yield of the reaction in order to throw light onto the efficiency of the process [7].

The reaction of 1-indanone-2-carboxylate *tert*-butyl ester with  $n\text{-C}_6\text{F}_{13}\text{I}$  in  $\text{PhCl}/\text{C}_8\text{F}_{18}$  as solvent has very recently been informed by Melchiorre and collaborators [8] under visible light irradiation (Scheme 3), in the presence of cinchona-derived phase-transfer catalyst PTC and  $\text{Cs}_2\text{CO}_3$  (2 equiv).

An array of electron-withdrawing substituents can be tolerated, as illustrated in Scheme 3 [8], independently of their ring-position. Perfluorinated chains of various lengths can be accommodated in the indanone scaffold in reasonable good chemical yields and high stereocontrol (*ee* ranging from 90% to 94%). Surprisingly,  $\text{CF}_3$ -containing quaternary stereocenters can be synthesized when  $\beta$ -ketoesters react with  $\text{CF}_3\text{I}$  (Scheme 3d).

Regarding the mechanism of this reaction, the authors hypothesize [8] that a propagation step as depicted in Scheme 4, is in operation. Excitation of the electron donor acceptor complex EDA of type A starts the chain reaction, generated when the chiral enolate B is added with  $\text{R}_\text{F}\text{I}$ . After visible-light irradiation, electron transfer ensues, and the electron-deficient  $\text{R}_\text{F}\cdot$  is produced by means of the

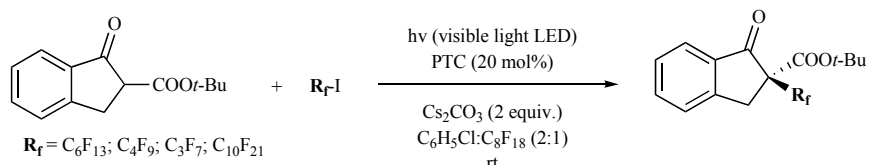
reductive scission of the C–I bond in C. When 1,4-dinitrobenzene (redox trap, 0.2 equiv) is employed, complete inhibition takes place. The electrophilic  $\text{R}_\text{F}\cdot$  is consequently trapped by the chiral enolate B in a stereocontrolled manner. The intermediate D then abstracts an iodine atom from C, regenerating  $\text{R}_\text{F}\cdot$  [9]. Due to the instability of adduct E, the product and the  $\text{PTC}^+$  catalyst are released.

### 2.1.2. Fluoroalkylation of $sp^2$ Carbon Atoms by POC

The hydrotrifluoromethylation of styrenes and unactivated aliphatic alkenes has been developed by Nicewicz and co-workers by means of an organic photoredox system [10]. Electron oxidation of  $\text{Na}_2\text{SO}_2\text{CF}_3$  (Langlois reagent) by photoredox catalyst *N*-methyl-9-mesitylacridinium achieves the transformation. The reaction can tolerate the presence of mono-, di- and trisubstituted aliphatic alkenes and styrenes, with high regioselectivity. The trifluoromethyl-substituted regioisomers obtained are exclusively anti-Markovnikov. The solvent used is a 9:1  $\text{CHCl}_3$  - TFE mixture. Methyl thio-salicylate is employed in small quantities as hydrogen donor for aliphatic alkenes; however, equivalent quantities of thiofenol are necessitated for the styrenyl alkenes. The trifluoromethylation reaction of alkenes is depicted in Scheme 5 [10].

A potential pathway is described in Scheme 6. The acridinium-derived photocatalyst is excited into a singlet manifold that undergoes intersystem crossing to a triplet state, which is able to oxidize the Langlois reagent and generate the electrophilic  $\text{CF}_3$  radical after the extrusion of  $\text{SO}_2$  [10]. Then, intermediate A is formed followed by the addition of the radical to the olefin (with an anti-Markovnikov selectivity). Trifluoroethanol supplies the hydrogen atom to the intermediate A. Radical intermediate B abstracts a hy-

## (a) General enantioselective photocatalytic reaction.



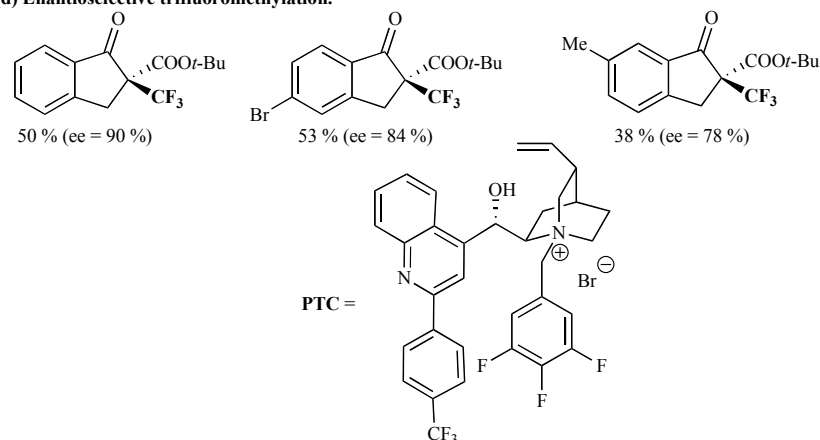
## (b) Substituent effect on the enantioselective photocatalytic reaction.

R	Yield (%)	ee (%)	R	Yield (%)	ee (%)
H	71	93	5-MeO	38	86
5-F	63	87	4-CF <sub>3</sub>	61	90
5-Cl	70	86	6-Me	55	83
5-Br	60	88	6-Br	55	83

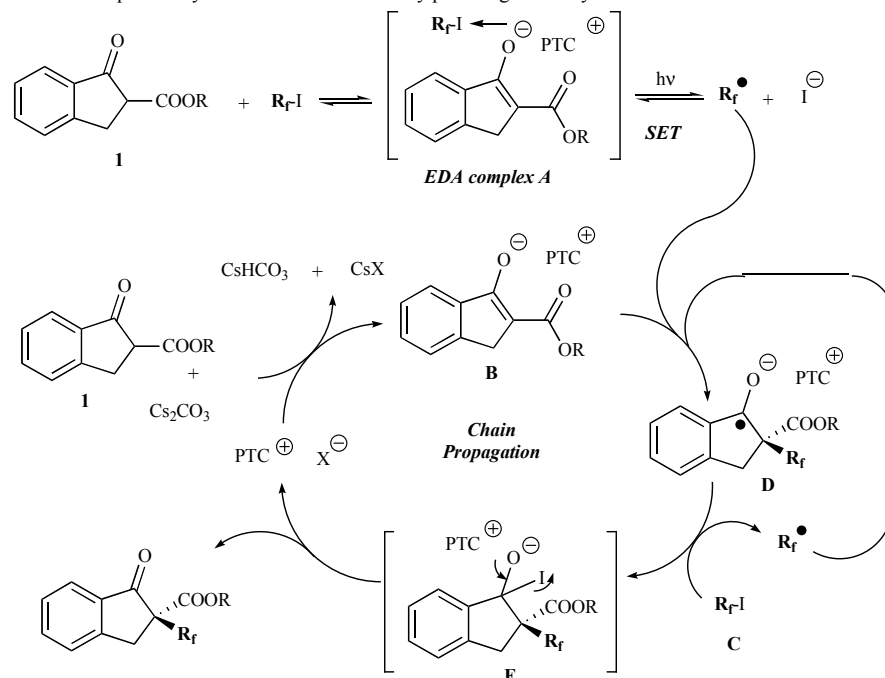
## (c) Reactivity of different perfluoroalkyl iodides.

R <sub>f</sub>	Yield (%)	ee (%)
C <sub>4</sub> F <sub>9</sub>	62	90
C <sub>10</sub> F <sub>21</sub>	68	93
C <sub>8</sub> F <sub>17</sub>	60	94

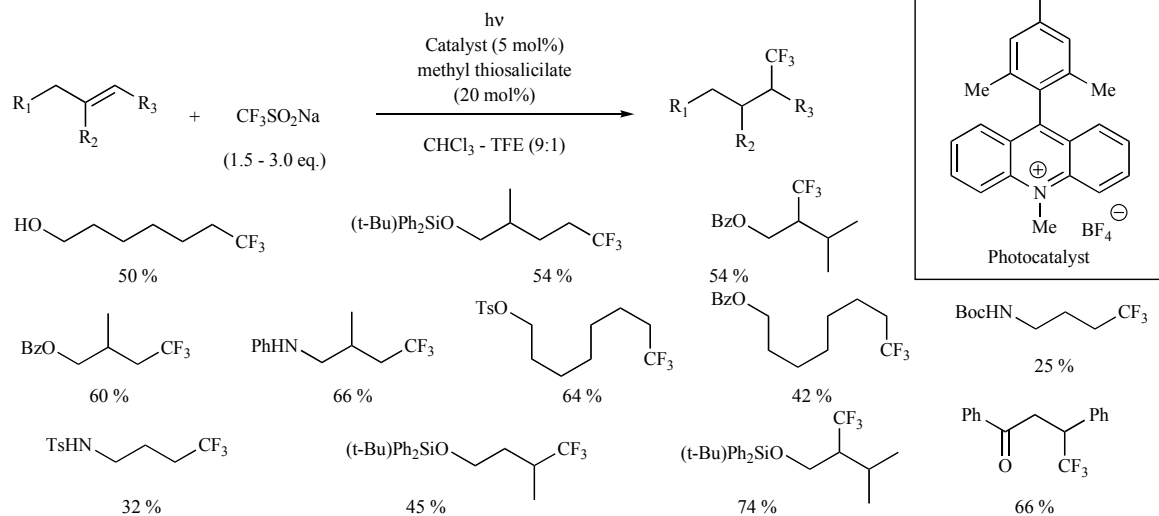
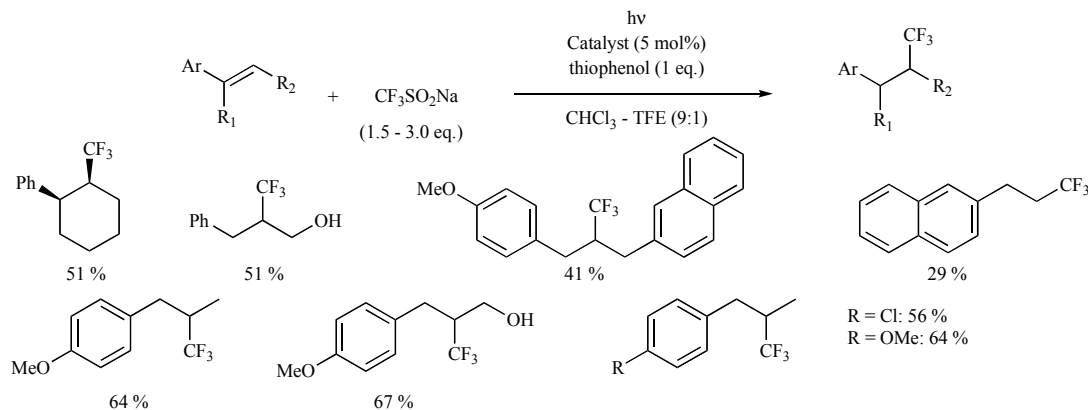
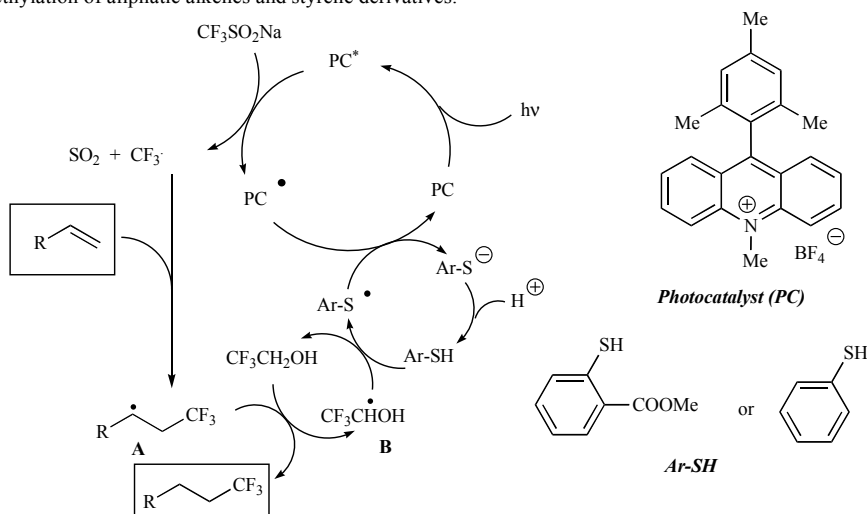
## (d) Enantioselective trifluoromethylation.



Scheme 3. Trifluoromethyl-substituted quaternary stereocenters achieved by photoorganocatalysis.



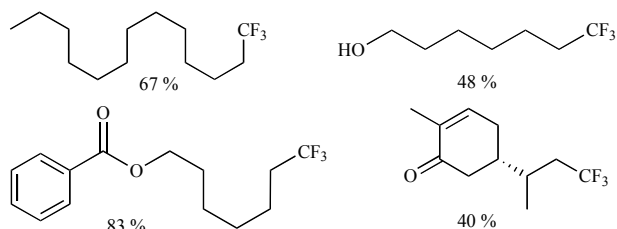
Scheme 4. Proposed reaction mechanism.

**(a) Substrate scope of the hydrotrifluoromethylation of aliphatic alkenes.****(b) Substrate scope of the hydrotrifluoromethylation of styrene derivatives.****Scheme 5.** Hydrotrifluoromethylation of aliphatic alkenes and styrene derivatives.**Scheme 6.** Proposed reaction mechanism of the hydrotrifluoromethylation of alkenes.

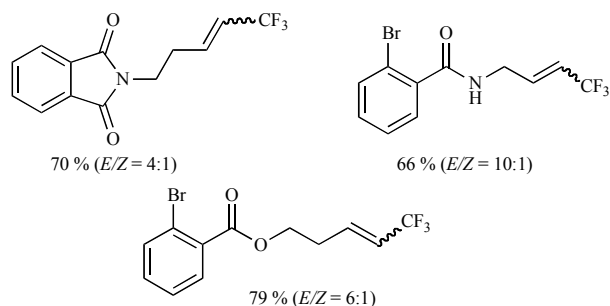
drogen atom from methyl salicylate or thiophenol, depending on the alkene derivatives employed, to render the phenylthiyl radical ( $Ar-S^\bullet$ ). The photocatalyst is then oxidized by thiyl radicals closing of the catalytic cycle and providing the formation of the corresponding thiolate ( $Ar-S^-$ ) which after a proton transfer process, regenerates the thiol. Another possible route would involve intermediate A reacting directly with a thiol [10].

Terminal alkenes and alkynes have been trifluoromethylated employing Methylene Blue (MB, 2 mol%) as the POC. This methodology has been investigated by Scaiano and co-workers employing the Togni(I)'s reagent as the  $CF_3$  radical source [11].  $N,N,N',N'$ -tetramethylethylene diamine TMEDA was employed as a sacrificial donor in DMF as solvent. The scope of the transformation is shown in Scheme 7.

## Hydrotrifluoromethylation of terminal alkenes.



## Hydrotrifluoromethylation of terminal alkynes.

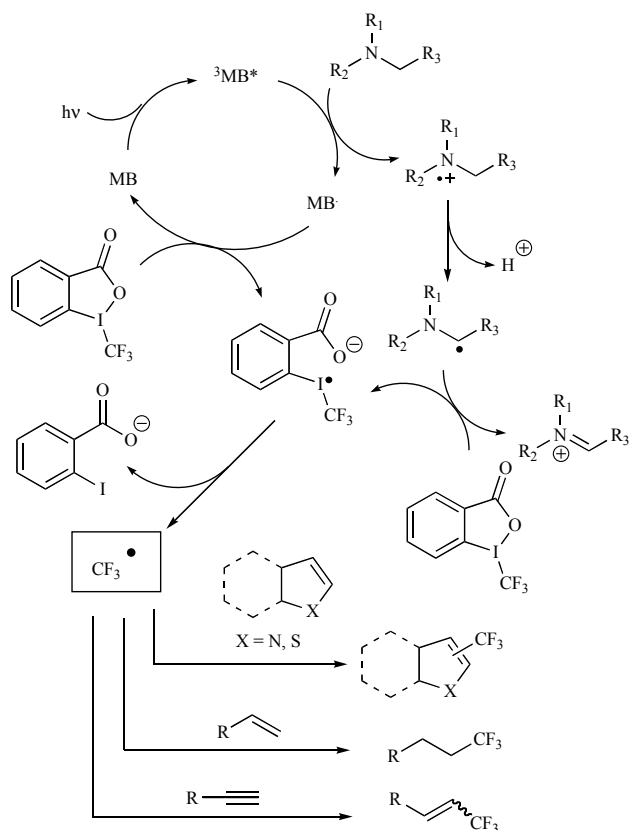


**Scheme 7.** Trifluoromethylation of heterocyclic compounds and hydrotrifluoromethylation of terminal alkenes and alkynes.

Products derived from the hydrotrifluoromethylation reaction of alkenes are obtained in moderate yields. However, the trifluoromethylated alkyne products obtained are observed in better yields as compared to those observed from alkenes and in a noticeable regioselectivity in favour of the *E* regioisomers, as depicted in Scheme 8.

The reaction mechanism proposed is illustrated in Scheme 8.

Irradiating the POC (MB) with wavelengths higher than 400 nm, affords the triplet excited manifold of the POC ( $^3\text{MB}^*$ ) that reacts with TMEDA to produce the semi reduced MB radical and an  $\alpha$ -amino radical.

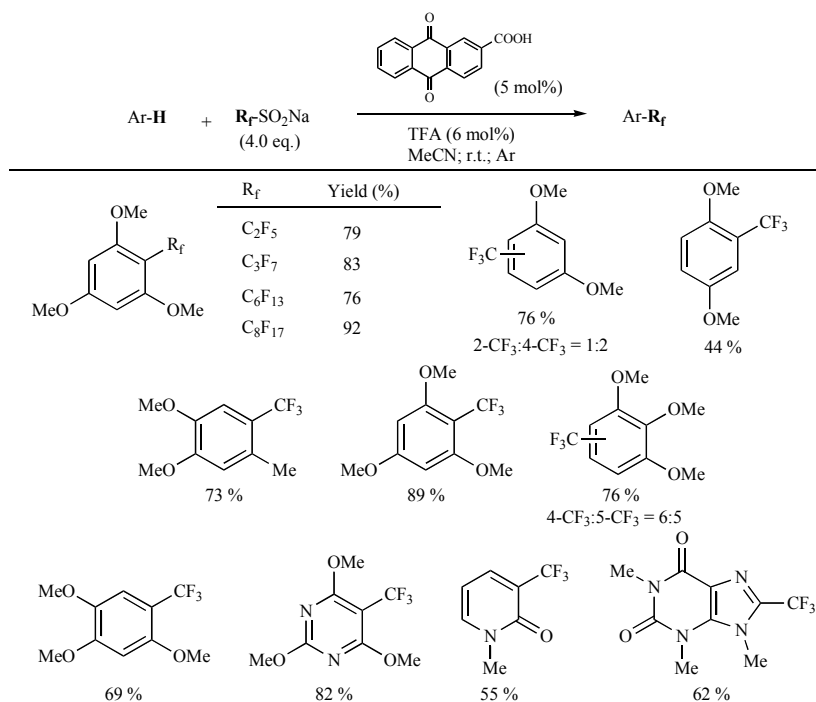


**Scheme 8.** Methylene blue (MB) as POC for the trifluoromethylation reaction.

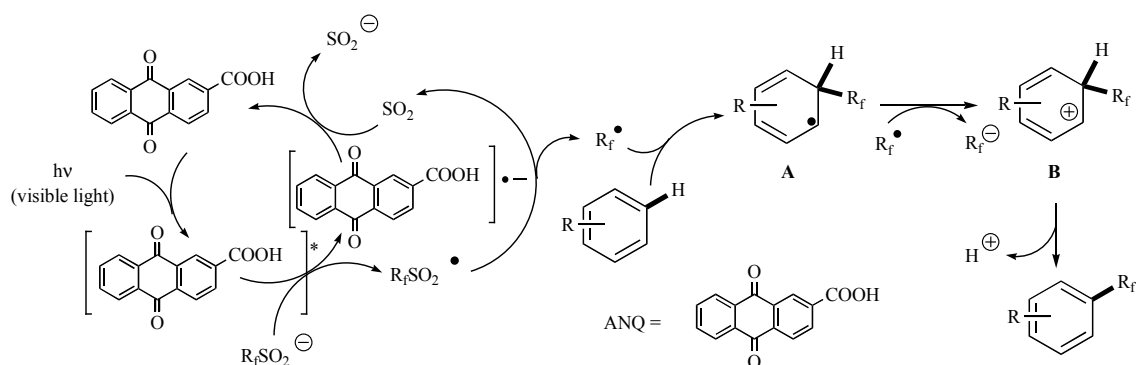
## 3. FLUOROALKYLATION OF AROMATIC SYSTEMS BY POC

## 3.1. Arenes

The metal-free photoredox perfluoroalkylation reaction of (hetero)arenes, through the use of perfluoroalkyl sulfinate salts

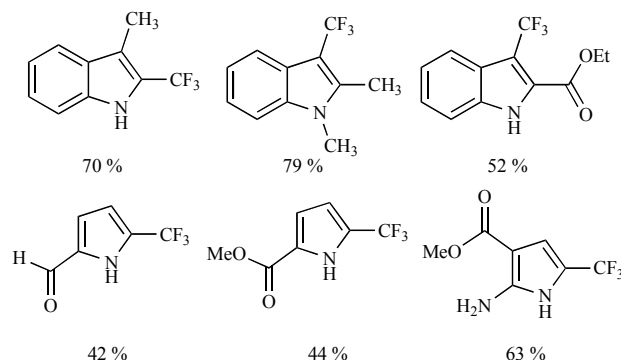


**Scheme 9.** Trifluoromethylation of organic substrates photoorganocatalyzed by anthraquinone-2-carboxylic acid.



**Scheme 10.** Proposed mechanism for the AQN-catalyzed trifluoromethylation of organic substrates.

#### Trifluoromethylation of heterocyclic compounds.



**Scheme 11.** Methylene Blue-photocatalyzed trifluoromethylation of heterocycles.

$R_fSO_2Na$ , in the presence of anthraquinone-2-carboxylic acid as POC and TFA as additive has been reported by Itoh and colleagues [12] in yields ranging from 70-90%. The authors [12] presented the scope and limitations of the reaction as shown in Scheme 9. Good product yields are obtained with electron-rich (hetero)arenes. Several  $NaSO_2R_f$  can be employed in the study. 1,3,5-Trimethoxybenzene can be substituted with  $C_2F_5$  and  $C_3F_7$  groups in good yields. Furthermore,  $NaSO_2C_6F_{13}$  and  $NaSO_2C_8F_{17}$  also react with 1,3,5-trimethoxybenzene to yield the corresponding products in good to high yields.

The proposed mechanism for the transformation is illustrated in Scheme 10 [12]. The POC anthraquinone-2-carboxylic acid AQN, can function from its ground and excited redox states as an electron transfer agent, which facilitates the generation of the electron-deficient  $R_f$  radicals; these radicals can oxidize the substrate.

The photoinduced electron transfer PET from  $R_fSO_2^-$  to AQN\* produces  $R_f\cdot$  and AQN $\cdot^-$  radicals based on their redox potentials. Rapid oxidation of AQN $\cdot^-$  by  $SO_2$  regenerates the ground state of AQN. The authors speculate that a possible reaction pathway takes into account addition of  $R_f$  radicals to the aryl moiety; then the  $R_f$  radical oxidizes radical A to cation B (Scheme 10) [12]. Another possibility is considering that  $R_f$  radicals abstract a hydrogen atom from A by, as is shown in Scheme 10.

The photocatalytic trifluoromethylation reaction of electron-rich heterocyclic compounds has been studied by Scaiano and co-workers employing Methylene Blue (MB) as the POC and the Togni(I)'s reagent as the  $CF_3$  radical source (*vide supra*) [10,11]. A stoichiometric quantity of TMEDA is necessary in the photoreaction. The solvent is DMF and the reaction is carried out under argon atmosphere at room temperature. Substituted indoles can be

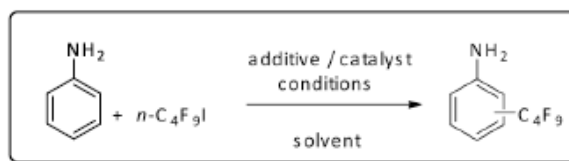
trifluoromethylated efficiently; however, no trifluoromethylation of the benzenoid moiety of the indole derivatives is noticed. Pyrroles and thiophenes can be trifluoromethylated in reasonable yields as well [11]. These results are summarized in Scheme 11. 3-methyl indole under photocatalysis and the Umemoto's reagent, affords the trifluoromethylated product in low yield (35%) [11].

#### 3.2. Amino-substituted Arenes. Mechanistic Interpretation

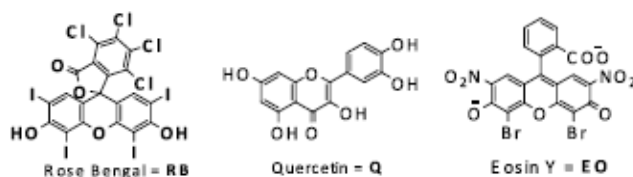
Recently, the perfluorobutylation of amino aromatic compounds has been accomplished by photoorganocatalysis with the aid of Rose Bengal RB, as initiator [13]. The authors [13] commenced the studies inspecting the role of the base [14] to produce  $C_4F_9$  radicals under dark reaction conditions, and their reaction with aniline, summarized in Table 1.

Variations in the base, solvent, temperature and stoichiometry have been studied (Table 1). The presence of air does seem to halt the reaction, thus having no effect in the initiation, and / or propagation (entry 13). Reaction conditions from entries 1,9, and 12 (Table 1), reveal that the methodology compromises substrate integrity, as large oligomeric material is formed and mass balance is incomplete (ca. 63%).

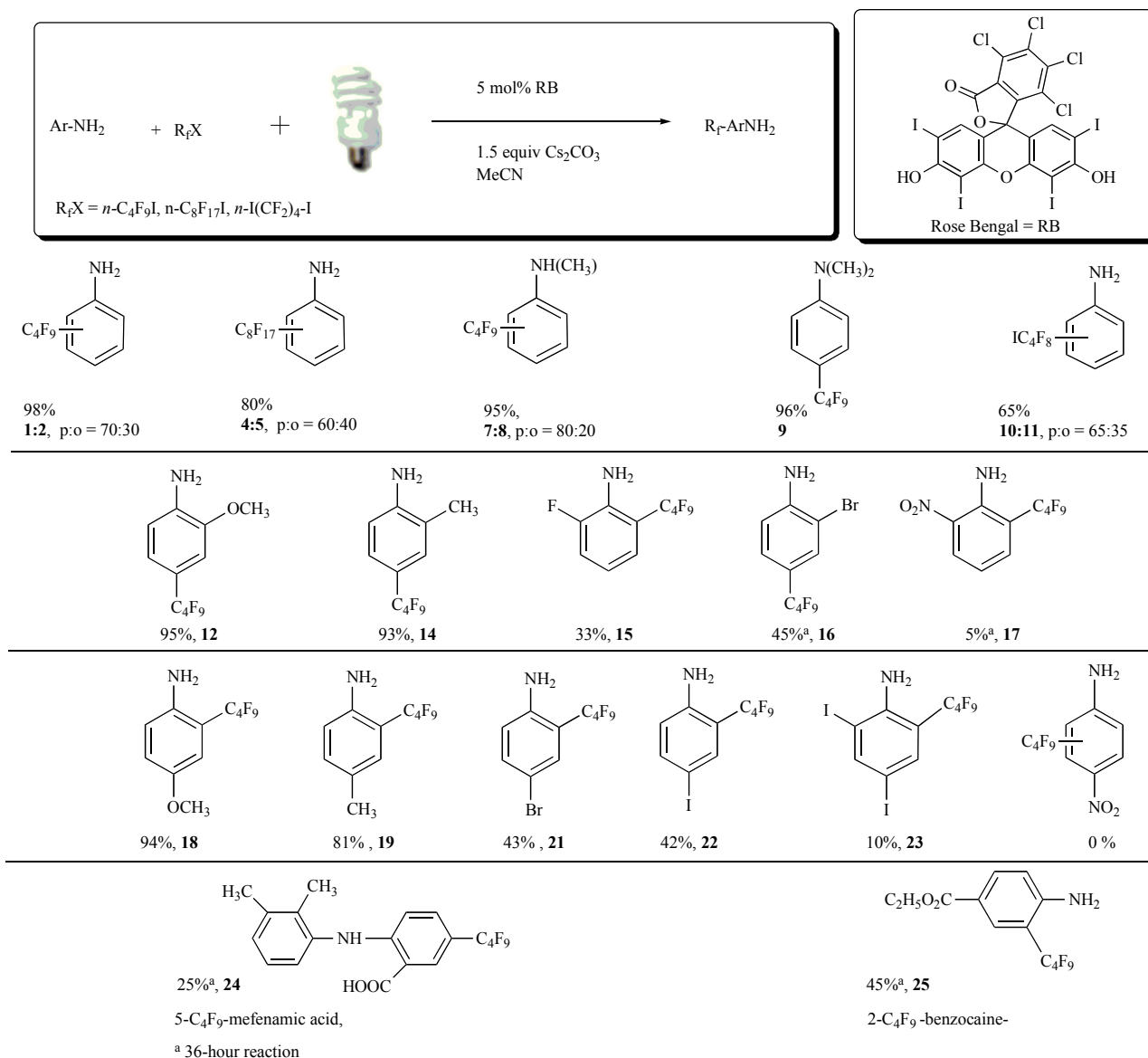
When using quercetin (Q) as POC, 25% yield of product is obtained (entry 14, Table 1). The authors [13] then employed other POCs such as Rose Bengal (RB) [15] (entry 15, Table 1), and eosine Y (EO) (entry 19, Table 1) and found good substitution yields with RB (52% yield of combined 1 and 2). After addition of  $Cs_2CO_3$  to the photocatalytic reactions of either Q (entry 16, Table 1) and RB (entry 17, Table 1), the substitution yields increased substantially, affording quantitative  $C_4F_9$ -substituted aniline with RB as PC in the presence of  $Cs_2CO_3$ . The illuminated reaction (entry 21, Table 1) affords 50% yield of combined substitution products 1 and 2 (*cf.* with entry 1, Table 1) indicating that room light is contributing to producing  $n-C_4F_9\cdot$  radicals in the presence of  $Cs_2CO_3$ , and absence of POC. The presence of air (entry 22, Table 1) affords very good yields of product (78% yield). The reaction [13] under solar light gives 91% yield of products 1,2 (entry 23, Table 1). The optimum reaction conditions consist of POC (RB),  $Cs_2CO_3$  in Ar-deoxygenated MeCN as solvent under a household fluorescent light bulb irradiation. When studying the rates of reaction the authors [13] observed the formation of the di-substituted 2,4-bis(perfluorobutyl)-aniline product 3 at the expense of the 2-(perfluorobutyl)-aniline 2 isomer, indicating that the *p*-isomer (*i.e.*: 4-(perfluorobutyl)-aniline, 1) is formed first, and disubstitution is originated from the *ortho*- $C_4F_9$ -substituted aniline 2. The reactions of secondary and tertiary aromatic amines lead to substitution products 7-9 in very good yields (Table 2). When  $I(CF_2)_4I$  is used

**Table 1.** Optimization of reaction conditions from reactions of aniline (0.2 mmol) with *n*-C<sub>4</sub>F<sub>9</sub>I, 3 equiv. (reaction time, additive, catalyst, solvent, temperature).

#	[An]:[R <sub>4</sub> ]:[additive]	Additive/ Catalyst (0.05 equiv)	T (°C)/ cond.	Solvent System	%(1+2) <sup>a</sup>
1	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / -	100/dark	1,4-dioxane	30
2	1:3:1.5	Na <sub>2</sub> CO <sub>3</sub> / -	100/dark	1,4-dioxane	-
3	1:3:-	- / -	100/dark	1,4-dioxane	-
4	1:3:1.5	CsF / -	100/dark	1,4-dioxane	< 5
5	1:3:1.5	CsF-Na <sub>2</sub> CO <sub>3</sub> / -	100/dark	1,4-dioxane	< 5
6	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / -	100/dark	1,4-dioxane:H <sub>2</sub> O	-
7	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / -	100/dark	THF	< 5
8	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / -	100/dark	MeCN	-
9	1:3:3	Cs <sub>2</sub> CO <sub>3</sub> / -	100/dark	1,4-dioxane	35
10	1:3:0.75	Cs <sub>2</sub> CO <sub>3</sub> / -	100/dark	1,4-dioxane	16
11	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / -	60/dark	1,4-dioxane	-
12	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / -	100/dark	1,4-dioxane <sup>b</sup>	30
13	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / -	100/dark	1,4-dioxane <sup>c</sup>	20
14	1:3:-	- / Q	RT / hv <sup>d</sup>	MeCN	25
15	1:3:-	- / RB	RT / hv <sup>d</sup>	MeCN	52
16	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / Q	RT / hv <sup>d</sup>	MeCN	50
17	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / RB	RT / hv <sup>d</sup>	MeCN	98
18	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / RB	RT / hv <sup>d</sup>	MeCN <sup>e</sup>	81
19	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / EO	RT / hv <sup>d</sup>	MeCN	62
20	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / RB	RT / hv <sup>d</sup>	H <sub>2</sub> O	< 5
21	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / -	RT / hv <sup>d</sup>	MeCN	50
22	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / RB	RT / hv <sup>d</sup>	MeCN <sup>e</sup>	78
23	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / RB	RT / hv <sup>f</sup>	MeCN	91
24	1:3:1.5	Cs <sub>2</sub> CO <sub>3</sub> / RB	RT / dark	MeCN	-



a.-yields determined by <sup>1</sup>H and <sup>19</sup>F RMN integration (combined 4-C<sub>4</sub>F<sub>9</sub> and 2-C<sub>4</sub>F<sub>9</sub> yields *para:ortho* = 70:30). b.-64-hour reaction. c.-without de-oxygenation. d.-60 watt fluorescent light bulb. e.-18-hour reaction f.-15 hour-accumulated sunlight exposure.

Table 2. C<sub>4</sub>F<sub>9</sub>-substituted aniline derivatives yields from the *Rose Bengal* photoredox organocatalysis.

instead of C<sub>4</sub>F<sub>9</sub>I, the aniline substituted with (CF<sub>2</sub>)<sub>4</sub>I **10** and **11** (with retention of the iodine atom), in a 65:35 isomeric ratio (Table 2). Table 2, shows the scope of the photocatalytic reaction with different aniline derivatives, substituted with electron withdrawing and releasing groups in the *ortho* and *para* positions of the aniline moiety (Table 2).

*Ortho*-substituted anilines with CH<sub>3</sub>O, CH<sub>3</sub>, F, Br, and NO<sub>2</sub> groups, afford C<sub>4</sub>F<sub>9</sub>- products (Table 2, products 12-17, respectively) with the C<sub>4</sub>F<sub>9</sub>-moiety at the 4-position of the ring with less or none substitution found at the 6-position of the ring. *Para*-substituted anilines with CH<sub>3</sub>O, CH<sub>3</sub>, Br, I, and 2,4-I<sub>2</sub> groups, afford major C<sub>4</sub>F<sub>9</sub>-group substitutions at the 2- position (and 6-position for 2,4-I<sub>2</sub>) of the ring (products 18-23, respectively, Table 2). Halo-substituted anilines also undergo a homolytic aromatic substitution HAS, and the C<sub>4</sub>F<sub>9</sub> products bear the original halogen atom(s) in the molecule intact. This observation is noteworthy, observing an orthogonal reactivity for haloarenes, with no *ipso* substitution of the bromine/iodine atom(s) under photocatalytic conditions. 2-nitro-substituted anilines can also afford the C<sub>4</sub>F<sub>9</sub>

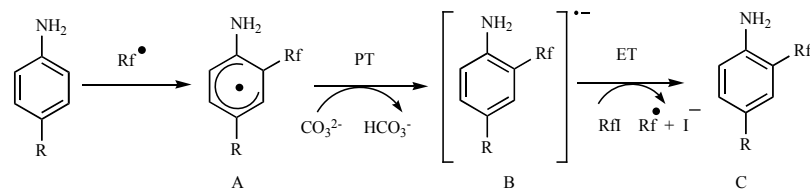
substitution product **17** as well (Table 2), however, the 4-nitro-aniline derivative is unreactive (Table 2). *p*-Toluidine affords a di-C<sub>4</sub>F<sub>9</sub>-substitution (product 20). Methoxy-substituted and methyl substituted anilines give C<sub>4</sub>F<sub>9</sub>-aniline derivatives in very good yields (products 12, 14, 18, and 19, 81-95%).

Anti-inflammatory drug mefenamic acid (*i.e.*: 2-((2,3-dimethylphenyl)amino) benzoic acid), gives product **24** in 25% yield (Table 2). Benzocaine (*i.e.*: ethyl-4-amino-benzoate), an anesthetic, affords 45% yield of the respective C<sub>4</sub>F<sub>9</sub>-substituted product **25**. A large scale (0.01 mol) reaction of benzocaine affords 30 % yield of **25**.

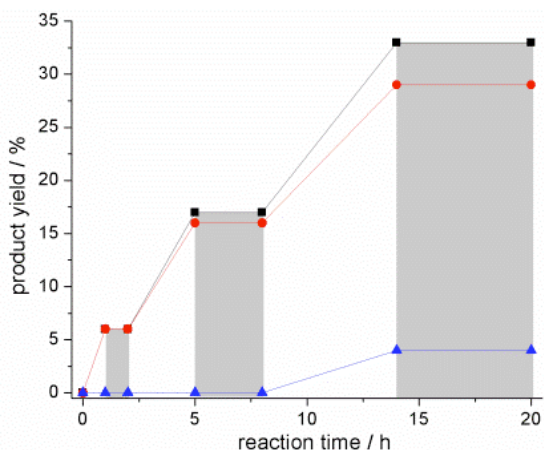
In order to elucidate the nature of the transition state / intermediate of the POC reaction, the ratio of rate constants for the reaction of anilines substituted in the *para*-position with different substituents, such as electron withdrawing and electron releasing groups, was studied.

The authors encountered that the relationship  $\log k_{p\text{-toluidine}}/k_{\text{ArNH}_2}$  is accelerated with electron releasing X groups on the aniline ring, implying that a stabilization of the transition state is





**Scheme 12.** Mechanism for the re-aromatization involving proton transfer-electron transfer (PT-ET).



**Fig. (1).** Plot of % product vs irradiation time. Lamp is maintained off in areas in shade. (■) % of isomer 1, (●) % of isomer 2, (▲) % of di-substitution.

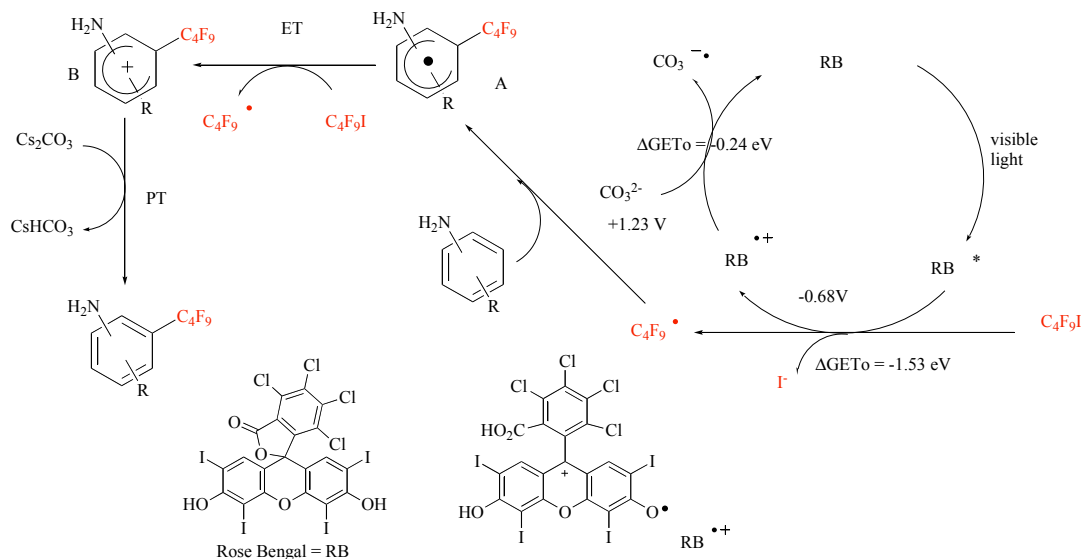
achieved with electron rich nuclei. *N,N*-dimethyl aniline in the presence of 1,4-dinitrobenzene (a radical anion scavenger) affords product 5 in yields as reported in Table 2. The photoreaction in the presence of TEMPO does not yield substitution product. Instead, the TEMPO- $C_4F_9$  adduct is obtained, indicating the presence of  $C_4F_9$  radicals. The fact that the presence of *p*-DNB also affords substitution product does not rule out the intermediacy of a radical anion, as this latter could probably be very short-lived. A likely mechanism can take into account the  $C_4F_9$ • radical attack on the aniline derivative, generating a  $C_4F_9$ -substituted cyclohexadienyl-radical A, which upon deprotonation by the base (PT,  $Cs_2CO_3$ ) affords a radical anion of the  $C_4F_9$ -substituted product B. Radical anion B could: *i.*-dissociate (in the case of Ar-I<sup>-</sup>) [16], *ii.*-undergo

an ET to *n*-I- $C_4F_9$  (to propagate the chain) and thermoneutral product C, *iii.*-ET to the substrate (chain termination), Scheme 12.

Notwithstanding, the acceleration of the  $C_4F_9$ -substitution reaction rates of anilines bearing electron releasing groups, indicates that besides the enthalpic factor considered for the Ar- $R_f$  bond formation (A, Scheme 12), there is a substituent effect on the rates of  $R_f$ -substituted anilines formation. An experiment turning on and off the lamp at times (Fig. 1) reveals that the reaction is light-initiated, and RB and light are needed for (enhanced) substitution to take place.

A proposed mechanism is depicted in Figure 2: a positively-charged intermediate/transition state develops, accounting for the differences in reaction rates. Room-light excitation of RB leads to RB\* which reduces *n*- $C_4F_9$ I, generating  $C_4F_9$ • radicals, and the radical cation of RB  $RB^{•+}$  [17] (Fig. 2).

RB could be acting as an initiator of the reaction, providing entry into the innate electron cycle, where  $C_4F_9$ • is re-generated. The fact that RB is re-generated by  $Cs_2CO_3$  closes and completes the initiation cycle. ET from RB\* to  $C_4F_9$ I ([18a,b]) can generate  $C_4F_9$ • radicals efficiently (and  $RB^{•+}$  radical cations) based on their redox potentials ( $E_{RB^{•+}/RB^*} = -0.68$  V vs SCE in MeCN [18b],  $E_{C_4F_9I/C_4F_9} = -1.27$  V [18c]). The  $\Delta G_{ET}$  for this process is -1.53 eV suggesting a quite favorable ET. A likely reaction pathway includes the radical addition of  $C_4F_9$ • to a position of the aniline nucleus, generating intermediate A (Fig. 2) oxidation to the cation intermediate B ensues (rate determining step). Taking into account that an acceleration of the substitution rates is observed with anilines having electron rich groups supports this mechanism. Deprotonation (PT, Fig. 2) affords  $C_4F_9$ -substituted aniline derivative. In the case of the PC quercetin Q, Markovic and collaborators [19] have observed that its radical cation,  $Q^{•+}$ , will rapidly be converted into Q



**Fig. (2).** Proposed mechanism for the RB photocatalyzed perfluoroalkylation of aniline derivatives.

in the presence of bases whose HOMO energies are higher than the SOMO energy of  $Q^+$ , meaning that Q cannot undergo the ET-PT mechanism leading to quercetin radical ( $Q^\cdot$ ) and proton  $H^+$ . Therefore, it is reasonable that in the proposed mechanism (entries 14, 16, Table 1),  $Q^+$  accepts an electron from the base ( $Cs_2CO_3$ ) and therefore forms Q thermoneutral (regenerating the PC) and carbonate radical anion ( $E(CO_3^{\cdot-}/CO_3^{2-}) = +1.23 \pm 0.15$  V on the basis of HOMO energy of the carbonate anion. This assumption can also apply to  $RB^{+\cdot}$  radical cation, which can therefore receive an electron from  $Cs_2CO_3$  in an analogous fashion as  $Q^+$  to regenerate RB. The fact that addition of  $Cs_2CO_3$  to the photocatalytic reactions (entries 17 & 18, Table 1) significantly improved the perfluorobutyl-lation yields could support the role of the base as an electron donor adjuvant to regenerate the catalyst. Furthermore, the photoinduced activation observed in the presence of  $Cs_2CO_3$  and absence of PC suggests the role of this base as an ET (photo)mediator (entry 21, Table 1). The authors calculated a value of -0.24 eV for the  $\Delta G_{ET}$  of this process (ET from  $CO_3^{2-}$  to  $RB^{+\cdot}$ ).

#### 4. CONCLUSIONS

Fluoroalkylation reactions can be conducted by photocatalysis, and this constitutes a new area of research, which through the use of ordinary laboratory dyes that absorb visible radiation or even solar light in the absence of transition metals, can trigger fluoroalkyl radical production that effect substitution reactions. The production of these radicals does not entail the use of chemical initiators. Photoorganocatalysis can therefore be regarded as a more environmentally friendly option to classical Ru or Ir catalysis, and future work should be aimed at employing dyes and visible light for the production of fluoroalkyl radicals capable of substituting organic substrates. Through the employment of organic photocatalysts, fluoroalkylation of  $sp^3$ ,  $sp^2$ , and  $sp$  carbon atoms can be accomplished, as well as the fluoroalkylation of (hetero)arenes.

#### CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

#### ACKNOWLEDGEMENTS

Declared none.

#### REFERENCES

- [1] (a) Ravelli, D.; Fagnoni, M.; Albini, A. Photoorganocatalysis. What for? *Chem. Soc. Rev.*, **2013**, *42*, 97-113. (b) For recent reviews on organocatalysis, see: i) Dondoni, A.; Massi, A. Asymmetric organocatalysis: From infancy to adolescence. *Angew. Chem. Int. Ed.*, **2008**, *47*, 4638-4660; ii) Seayad, J.; List, B. Asymmetric organocatalysis. *Org. Biomol. Chem.*, **2005**, *3*, 719-724; iii) Berkessel, A.; Grger, H. Asymmetric Organocatalysis, Wiley-VCH, Weinheim, 2005; iv) Dalko, P.I. Enantioselective Organocatalysis, Wiley-VCH, Weinheim, 2007. (c) For some selected recent applications, see: i) Hong, B.C.; Kotame, P.; Tsai, C.W.; Liao, J.H. Enantioselective total synthesis of (+)-conicol via cascade three-component organocatalysis. *Org. Lett.*, **2010**, *12*, 776-779. ii) Jakubec, P.; Cockfield, D.M.; Dixon, D.J. Total synthesis of (-)-nakadomarin A. *J. Am. Chem. Soc.*, **2009**, *131*, 16632-16633. Review: iii) Marcia de Figueiredo, R.; Christmann, M. Organocatalytic synthesis of drugs and bioactive natural products. *Eur. J. Org. Chem.*, **2007**, (16), 2575-2600. (d) Barata-Vallejo, S.; Bonesti, S.M.; Postigo, A. Photocatalytic fluoroalkylation reactions of organic compounds. *Org. & Biomol. Chem.*, **2015**, *13*, 11153-11183
- [2] (a) Neumann, M.; Földner, S.; König, B.; Zeitler, K.; Metal-free, cooperative asymmetric organophotoredox catalysis with visible light. *Angew. Chem. Int. Ed.*, **2011**, *50*, 951-954. (b) Neumann, M.; Zeitler, K. Application of micro-flow conditions to visible light photoredox catalysis. *Org. Lett.*, **2012**, *14*, 2658-2661.
- [3] (a) Shimidzu, T.; Iyoda, T.; Koide, Y. An advanced visible-light-induced water reduction with dye-sensitized semiconductor powder catalyst. *J. Am. Chem. Soc.*, **1985**, *107*, 35-41; (b) Neckers, D.C.; Valdes-Aguilera, O.M. Photochemistry of the xanthenes dyes. *Adv. Photochem.*, **1993**, *18*, 315-394.
- [4] (a) Labat, F.; Ciofini, I.; Hratchian, H.P.; Frisch, M.; Raghavachari, K.; Adamo, C. First principles modeling of eosin-loaded ZnO films: A step towards the understanding of dye-sensitized solar cell performances. *J. Am. Chem. Soc.*, **2009**, *131*, 14290 - 14298; (b) Jhonsi, M.A.; Kathiravan, A.; Renganathan, R. Photoinduced interaction between xanthenes dyes and colloidal CdS nanoparticles. *J. Mol. Struct.*, **2009**, *921*, 279 - 284.
- [5] The high-energy intermediate of eosin  $Y^{\cdot-}EY^*$  can function as an oxidant, showing similar redox properties as photoexcited  $[Ru(bpy)_3]^{2+}$ : cf.  $E^0(Y^{\cdot-}/EY^*) = +0.83$  V vs.  $E^0(Ru^{2+}/Ru^{\cdot+}) = +0.79$  V vs. SCE.
- [6] Remarkably, in contrast to most photocatalytic processes MacMillan's system does not require any sacrificial oxidant or reductant by its design; both oxidation and reduction steps are productive and lead to the formation of the desired product.
- [7] For a recent discussion on the normalization of photocatalytic reactions, see: Maschmeyer, T.; Che, M. Catalytic aspects of light-induced hydrogen generation in water with TiO<sub>2</sub> and other photocatalysts: A simple and practical way towards a normalization? *Angew. Chem. Int. Ed.*, **2010**, *49*, 1536-1539.
- [8] Wozniak, L.; Murphy, J.J.; Melchiorre, P. Photo-organocatalytic enantioselective perfluoroalkylation of  $\beta$ -ketoesters. *J. Am. Chem. Soc.*, **2015**, *137*, 5678-5681.
- [9] Petrik, V.; Cahard, D. Radical trifluoromethylation of ammonium enolates. *Tetrahedron Lett.*, **2007**, *48*, 3327.
- [10] (a) Wilger, D.J.; Gesmundo, N.J.; Nicewicz, D.A. Catalytic hydrotrifluoromethylation of styrenes and unactivated aliphatic alkenes via an organic photoredox system. *Chem. Sci.*, **2013**, *4*, 3160-3165. (b) Morse, P.D.; Nicewicz, D.A. Divergent regioselectivity in photoredox-catalyzed hydrofunctionalization reactions of unsaturated amides and thioamides. *Chem. Sci.*, **2015**, *6*(1), 270-274.
- [11] Pitre, S.P.; McTiernan, C.D.; Ismaili, H.; Scaiano, J.C.; Metal-free photocatalytic radical trifluoromethylation utilizing methylene blue and visible light irradiation. *ACS Catal.*, **2014**, *4*, 2530-2535.
- [12] Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A. Metal-free direct C-H perfluoroalkylation of arenes and heteroarenes using a photoredox organocatalyst. *Adv. Syn. & Cat.*, **2013**, *355*, 2203-2207.
- [13] Barata-Vallejo, S.; Yerien, D.E.; Postigo, A. Benign perfluoroalkylation of aniline derivatives through photoredox organocatalysis under visible-light irradiation. *Eur. J. Org. Chem.*, **2015**, (36), 7869-7875.
- [14] Nappi, M.; Bergonzini, G.; Melchiorre, P. Metal-free photochemical aromatic perfluoroalkylation of  $\alpha$ -cyano arylacetates. *Angew. Chem. Int. Ed.*, **2014**, *53*, 4921.
- [15] (a) Lambert, C.; Sarna, T.; Truscott, G. Rose bengal radicals and their reactivity. *J. Chem. Soc. Faraday Trans.*, **1990**, *86*, 3879-3882. (b) Thorson, R.A.; Woller, G.R.; Driscoll, Z.L.; Geiger, B.E.; Moss, C.A.; Schlapper, A.L.; Speetzen, E.D.; Bosch, E.; Erdélyi, M.; Bowling, N.P. Intramolecular halogen bonding in solution: 15N, 13C, and 19F NMR studies of temperature and solvent effects. *Eur. J. Org. Chem.*, **2015**, (8), 1685-1695; (c) Cao, H.P.; Xiao, J.C. Fluoroalkylation of aromatics: An intramolecular radical cyclization of 4-chloro-1,1,2,2,3,3,4,4-octafluorobutylbenzenes. *J. Fluorine Chem.*, **2006**, *127*, 1079-1086.
- [16] (a) Yi, H.; Jutand, A.; Lei, A. Evidence for the interaction between tBuOK and 1,10-phenanthroline to form the 1,10-phenanthroline radical anion: A key step for the activation of aryl bromides by electron transfer. *Chem. Commun.*, **2015**, *51*, 545-548. (b) Pierini, A.B.; Duca, J.S. Theoretical study on haloaromatic radical anions and their intramolecular electron transfer reactions. *J. Chem. Soc. Perkin Trans. 2*, **1995**, *9*, 1821-1828.
- [17] (a) Armstrong, D.A.; Waltz, W.L.; Rauk, A. Carbonate radical anion — Thermochemistry. *Can. J. Chem.*, **2006**, *84*, 1614-1619. (b) Liu, H.; Feng, W.; Kee, C.W.; Zhao, Y.; Leow, D.; Pan, Y.; Tan, C.H. Organic dye photocatalyzed  $\alpha$ -oxyamination through irradiation with visible light. *Green Chem.*, **2010**, *12*, 953-956.
- [18] (a) Lambert, C.; Kochevar, I.E. Electron transfer quenching of the rose bengal triplet state. *Photochem. Photobiol.*, **1997**, *66*, 15-25; (b) Burget, D.; Fouassier, J.P.; *J. Chem. Soc. Faraday Trans.*, **1998**, *94*, 1849-1854. (c) Andrieux, C.P.; Clis, L.G.; Medebielle, M.; Pinson, P.; Saveant, J.M. Outer-sphere dissociative electron transfer to organic molecules: A source of radicals or carbanions? Direct and indirect electrochemistry of perfluoroalkyl bromides and iodides. *J. Am. Chem. Soc.*, **1990**, *112*, 3509-3520.
- [19] Markovic, Z.; Amic, D.; Milenkovic, D.; Dimitri-Markovic, J.M.; Markovic, S. Examination of the chemical behavior of the quercetin radical cation towards some bases. *Phys. Chem. Chem. Phys.*, **2013**, *15*, 7370-7378.